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II. 1. Lipoprotein receptors

Lipoprotein(a) in Internal Medicine

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Lipoprotein(a) - Lp(a) - resembles LDL in being cholesterol rich but it is distinguished by its content of a particular apolipoprotein apo(a). It exhibits genetically determined size heterogeneity which is inversely associated with plasma concentrations of Lp(a), accounting for approximately 50% of its variance in Western populations. However, other genetic and environmental factors also might influence Lp(a) homeostasis. Turnover studies in human subjects have suggested that Lp(a) plasma concentrations correlate strongly with its production but not with its fractional catabolic rate. High Lp(a) concentrations have been associated with coronary heart disease especially if LDL cholesterol is also elevated. However, there are also opposite reports and to our knowledge so far no data from a prospective cohort study on the CHD risk derived from Lp(a) are available nor do we have much knowledge on Lp(a) concentrations in various diseases.

This communication will present prospective data on Lp(a) derived from a prospective cohort study (GRIPS) performed on more than 5,000 male subjects (aged 40-60 yrs), observed during a 5-year follow-up period.

Also, comprehensive data will be presented for age distribution (new borns to 95 yrs) of Lp(a) concentrations in approximately 1100 healthy subjects (50% females > 20 yrs) as well as for concentrations and fluctuations of Lp(a) in various diseases: metabolic, endocrinologic, kidney, liver, autoimmune, inflammatory, thrombotic diseases, myocardial infarction and cancer.

Methods

Serum Lp(a) concentrations were measured for the GRIPS study in samples taken in 1982 and stored at -70°C until measurement in 1991. Samples taken from controls and patients of various diseases were analyzed within 24 hours after drawing. All measurements were performed by nephelometry (Behring, Marburg, FRG), Laurell technique (Immuno, Heidelberg, FRG) and ELISA (Immuno) in parallel using monospecific antisera against Lp(a). All analyses were run in duplicate using the procedures recommended by the manufacturer; the standard material and control sera were purchased from Immuno. Standard quality control was performed on each series; Lp(a) concentrations are expressed as milligram per deciliter total particle mass.

Results

The influence of sex on the Lp(a) concentration was determined in approximately 900 healthy subjects ≥ 20 yrs of age (50% females). No difference became evident over all age classes from 20 to 95 yrs, with a median of 10 mg/dl for females and 9 mg/dl for males. This is in contrast to marked sex differences in apo A1 concentrations in the same group which revealed a median of 161 mg/dl for females, but 142 mg/dl for males.

To study the influence of age on the Lp(a) concentration, Lp(a) was measured in 54 cord blood samples of newborns and in sera of approximately 450 healthy males and 450 healthy females ranging from 1 to 95 yrs. Concentrations of Lp(a) were below 5 mg/dl in all cord blood samples but showed a continuous rise for the first half year

after birth, reaching a steady state which maintained up to puberty. This was followed by a second rise to reach adult concentrations by the age of 20. After this no influence of age was observed up to the age of 95 years neither for the median (9 mg/dl) nor for the distribution as reflected by the 90% percentile. Again, this is in striking contrast to the influence of age on apoprotein B which shows a constant rise up to the age of 45 yrs followed first by a steady state and then by a marked decline beyond the age of 70.

With the exception of a weak but statistically significant correlation of Lp(a) with total cholesterol and apo B, no correlation was found between Lp(a) concentration and other lipoproteins or any of the known cardiovascular risk factors (see Tab. 1). In particular no correlation was found between LDL concentration and Lp(a) neither in the total reference group of GRIPS (n = 5132) nor in subgroups stratified for Lp(a) or LDL concentrations respectively.

Table 1. Relationship of Lp(a) to Life Style and CHD Risk Ractors. Data from the GRIPS Study Group, n = 5387 men, 40-59 yrs

		n	Median	10-90%
BME	< 25 kg/m²	1876	9	< 5-43
	25-29 kg/m²	2998	9	< 5-42
	≥ 30 kg/m²	512	10	< 5-42
Smoking	no	3401	9	< 5-43
	yes	1985	9	< 5-43
Alcohol	never	603	11	< 5-42
	occasionally	1680	9	< 5-43
	regularly	3103	9	< 5-42
Physical Activity				
	none	3282	9	< 5-42
	occasionally/ regularly	2104	9	< 5-42

		n	Median	10-90%
Hypertension (WHO definition)				
Blood Pressure	normal	2701	9	< 5-43
	border line	1637	9	< 5-42
	increased	1048	9	< 5-41
Hyperglycemia				
Glucose	< 120	4731	9	< 5-42
	120-149	477	9	< 5-44
	≥ 150	178	8	< 5-45
Familial MI History				
	no	4890	9	< 5-42
	yes	496	11	< 5-46

Table 2. Lp(a) Concentration in Various Pathological Conditions vs. Normals

Diminished	n	Increased	n
Breast CA	286	Acute Phase Reaction:	
Gastric CA	61	elevated α1, α2 globulin	50
Pancreatic CA	58	Diabetes	40
Myasthenia gravis	50	Liver Cirrhosis	
Septicemia	19	without Cholestasis	15
Cholestasis	15	Pregnancy	11
Hepatitis	5	Post MI Period	5
		PTCA	61
		Renal Insufficiency	79
No Difference		Shunt Thrombosis	16
Thyroid Dysfunction	265		
Chronic Polyarthritis	67		
Sjörgren Syndrome	21		

Table 3. Ranking of MI Risk Factors (GRIPS).
Multivariate Logistic Regression Analysis

	Variable	Categories	Chi²	(p-Value)	Odds Ratio
1	LDL Cholesterol	< 150/-189/ ≥ 190 mg/dl	90	< 0.0001	3.6 (= 13 total)
2	Familial MI History	none/pos.	29	< 0.0001	4.0
3	Age	< / ≥ 50 yrs	16	< 0.001	2.3
4	Lp(a)	< / ≥ 30 mg/dl	16	< 0.001	2.5
5	HDL Cholesterol	≥ / < 35 mg/dl	15	< 0.001	2.5
6	Smoking	no/yes	6	0.01	1.7
7	Blood Pressure	elevated, y/n	5	0.03	1.7
8	Blood Glucose	< / ≥ 120 mg/dl	4	< 0.05	1.7

Measurement of Lp(a) in various diseases (see Tab. 2) revealed situations with trends to decreased or increased concentrations respectively and some with unchanged values as compared to healthy subjects. Significantly lower Lp(a) concentrations (median 6) were found in patients with gastric cancer (n = 61) as compared to the normal population (n = 911). In 6 patients with gastric cancer Lp(a) and apo B concentrations were followed during the course of the disease and correlated to the CEA tumor marker. While apo B showed a dramatic decrease along with the duration and progression (CEA increase) of this disease, Lp(a) maintained its concentration unaffected. The same pattern was found (n=58) for patients with cancer of the pancreas, revealing a median of 4 mg/dl as compared to 9 mg/dl of the healthy subject group; again, no change of Lp(a) during the course of the disease was observed. The strong influence of the thyroid gland on lipid, lipoprotein and apoprotein concentrations is well established. In our study we measured Lp(a) in over 250 patients with a dysfunction of the thyroid gland. While all other lipids, lipoproteins and apoproteins were strongly and inversely related to thyroxine values, no relevant alterations of Lp(a) were observed in either hyperthyroidism or hypothyroidism.

A significant increase in plasma Lp(a) concentrations was observed after myocardial infarction with a peak value 8 days after the event, resembling a low phase reaction very much in parallel with ceruloplasmin. Usually 2 weeks after the event Lp(a) concentrations are closely back to normal.

With regard to the question of Lp(a) as an independent risk factor for atherosclerotic diseases, the data of our prospective cohort study (GRIPS) were analyzed, based on a 5 year follow-up of more than 5,000 initially healthy male subjects (age 40-59 yrs). Participants who developed an atherosclerotic disease during the follow-up period (incidence group) had higher median values of Lp(a) at the initial examination as compared to those remaining healthy (reference group): myocardial infarction (MI) 15 vs. 9, chronic coronary heart disease 13 vs. 9, stroke 15 vs. 9, peripheral arterial vascular disease 13 vs. 9 mg/dl. However, significant differences in comparison to the reference group were only seen for the MI incidence group.

Univariate as well as multivariate logistic regression analysis revealed Lp(a) ranking in its predictive power close to HDL cholesterol but lower than LDL cholesterol or familial history of myocardial infarction (see Tab. 3).

Lp(a) accelerates very significantly the atherogenic influences of LDL cholesterol, whereas the impact of Lp(a) is significantly potentiated by low HDL cholesterol, elevated LDL cholesterol or positive family history for MI, to a lesser extent also by smoking, hypertension or diabetes mellitus.

Conclusion

1. Besides genetically determined Lp(a) isoforms the role of other factors influencing the plasma Lp(a) concentration remains unclear. Important determinants which alter or change the plasma LDL levels have no significant effect on Lp(a).
2. A potential inverse relationship or association that exists between Lp(a) levels and certain malignant diseases needs further clarification.
3. Lp(a) ranks similar to HDL but lower than LDL as risk factor for atherosclerotic vessel disease. This applies in particular for the acute events (MI, stroke) and to a lesser extent for chronic forms (CHD and PAVD).
4. After puberty the distribution pattern of Lp(a) does not change with age. It thus appears that Lp(a) does not influence life expectancy.

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